Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis

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Summary

Background The full extent to which childhood pneumococcal conjugate vaccines (PCV) can indirectly reduce illness in unvaccinated populations is not known. We aimed to estimate the magnitude and timing of indirect effects of PCVs on invasive pneumococcal disease.

Methods In this systematic review and meta-analysis, we searched bibliographic databases for non-randomised quasi-experimental or observational studies reporting invasive pneumococcal disease changes following PCV introduction in unvaccinated populations (studies published Sept 1, 2010, to Jan 6, 2016), updating the previous systematic review of the same topic (studies published Jan 1, 1994, to Sept 30, 2010). Two reviewers extracted summary data by consensus. We used a Bayesian mixed-effects model to account for between-study heterogeneity to estimate temporal indirect effects by pooling of invasive pneumococcal disease changes by serotype and serogroup.

Findings Data were extracted from 70 studies included in the previous review and 172 additional studies, covering 27 high-income and seven middle-income countries. The predicted mean times to attaining a 90% reduction in invasive pneumococcal disease were 8·9 years (95% credible interval [CrI] 7·8–10·3) for grouped serotypes contained in the seven-valent PCV (PCV7), and 9·5 years (6·1–16·6) for the grouped six additional serotypes contained in the 13-valent PCV (PCV13) but not in PCV7. Disease due to grouped serotypes contained in the 23-valent pneumococcal polysaccharide vaccine (PPV23) decreased at similar rates per year in adults aged 19–64 years (relative risk [RR] 0·85, 95% CrI 0·75–0·95) and 65 years and older (0·87, 0·84–0·90). However, we noted no changes in either group in invasive pneumococcal disease caused by the additional 11 serotypes covered by PPV23 but not PCV13.

Interpretation Population childhood PCV programmes will lead, on average, to substantial protection across the whole population within a decade. This large indirect protection should be considered when assessing vaccination of older age groups.

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Introduction

Invasive pneumococcal disease due to *Streptococcus pneumoniae* infection is a major source of ill health worldwide, especially in children under 5 years, older people, and individuals with risk factors (ie, splenic dysfunction, heart disease, or immunodeficiency).[1–4] Childhood vaccination is recommended by WHO and is increasingly implemented across the world.[5] The first pneumococcal conjugate vaccine (PCV) was seven-valent (PCV7), was licensed in 2000, and has since been replaced by ten-valent (PCV10) or 13-valent (PCV13) versions. In some countries, mostly high-income countries, the 23-valent pneumococcal polysaccharide vaccine (PPV23) was introduced in adults earlier than childhood PCVs.[6–9]

Routine use of childhood PCVs has substantially changed the epidemiology of pneumococcal disease. In vaccinated young children, disease due to serotypes included in the vaccines has been reduced to negligible levels.[10] Decreases in both disease and carriage have also been observed in unvaccinated groups in different countries.[11–14] However, in unvaccinated population age groups, especially older adults, substantial residual disease and deaths due to serotypes covered by both childhood and adult vaccines remain.[15,16] Also, in some settings, disease due to serotypes not covered by these vaccines has increased.[17–21]

In addition to childhood PCVs and adult PPV23 programmes, the use of conjugate vaccines in healthy and immunocompromised adults is effective. A randomised placebo-controlled trial[15,22] of PCV13 use conducted during 2008–13 in the Netherlands among 85 000 adults 65 years and older showed an efficacy of 75·0% (95% CI 41·4–90·8) against vaccine-type invasive pneumococcal disease, 45·6% (21·8–62·5) against all vaccine-type pneumonia, and 45·0% (14·2–65·3) against vaccine-type non-bacteraemic pneumonia. Previously, PCV7 showed an efficacy of 75% (29–92) for prevention of invasive pneumococcal disease in HIV-infected adults in Malawi.[23] In view of the efficacy of PCV13 in adults,[15,22] some countries such as the USA introduced this vaccine

Research in context

Evidence before this study

Strong evidence shows that there are direct and herd immunity effects of pneumococcal conjugate vaccines (PCVs). However, the protective effect of existing vaccination programmes have not been systematically quantified. A previous systematic review focused on the seven-valent pneumococcal vaccine (PCV7) only, which has since been replaced by the 13-valent pneumococcal vaccine (PCV13) in most countries. Since 2010, many more countries have introduced the PCV13 vaccine. Data from individual studies have become available from different countries, with a wide range of programme maturity, vaccination schedules, and coverage.

Added value of this study

We have used data for disease changes due to serotypes covered by conjugate vaccines to provide quantitative estimates of the expected rate of development of herd immunity. Countries with mature PCV7 programmes allowed the evaluation of the long-term effects. We showed that similar early effects on disease due to the additional six serotypes in PCV13 suggest that long-term effects will follow a similar course—ie, a 90% reduction in disease burden due to the covered serotypes among adults through herd immunity can be achieved within a decade of establishing a sustained childhood programme. Disease burden reduction is more rapid with higher vaccine coverage but variations in schedule are less important.

Implications of all the available evidence

The large indirect protection of childhood vaccinations programmes should be considered when assessing vaccination of older age groups, an issue that is pertinent in high-income countries, as well as informing priorities in the childhood programme. The evidence gap is substantial for low-income countries on the impact of childhood pneumococcal vaccination on disease in age groups not eligible to be vaccinated. Because these countries are increasingly undertaking childhood vaccination programmes, research to assess the indirect effects in these settings is particularly relevant.

into their adult immunisation programme, in addition to PPV23, with authorities in the USA due to review the programme in 2018. By contrast, several developed countries have not introduced PCV13 into their adult immunisation programmes.[16]

See Online for appendix

In this systematic review and meta-analysis, we aim to assess the extent to which childhood pneumococcal vaccination affects disease incidence in adult populations and the time course of this effect when childhood vaccination programmes are introduced. This work is motivated by both the need to improve understanding of the full effects of childhood programmes and the need to inform policy decisions on the use of PCVs or PPV23 in adult populations that have an effective childhood PCV13 programme. The findings should inform the existing immunisation policy discussions around the cost-effectiveness of introducing PCVs into adult immunisation programmes to speed up elimination of residual disease due to vaccine serotypes.[24,25]

Methods

Search strategy and selection criteria

We report this systematic review and meta-analysis in accordance with the PRISMA statement.[26] To identify relevant articles, we updated a list of studies published between Jan 1, 1994, and Sept 30, 2010, reported by Davies and colleagues[27] in a systematic review of indirect protection effects of PCVs. We searched for additional English language studies in Medline, Embase, and Web of Science for the period between Sept 1, 2010, and Jan 6, 2016, and included the terms "pneumococcus or pneumococcal", "vaccine or vaccination or immunisation or immune", and "pneumonia or invasive or meningitis or carriage or colonisation"—ie, we used the same free text terms in the search strategy reported by Davies and colleagues,[27] plus additional Medline and Embase subject headings (appendix). We supplemented these studies by searching the abstract book of the 9th International Symposium on Pneumococci and Pneumococcal Disease (ISPPD-9, held in Hyderabad, India on March 9–13, 2014) for any relevant abstracts.

Because our study was an extension of an existing review, we did not register our study in any database. Studies were eligible if they were designed as non-randomised quasi-experimental or observational studies with or without comparator group (eg, pre-test or post-test, time series, multiple interrupted time series, population-based or laboratory-based surveillance), and if the population (of any age or sex) considered was not targeted for PCV vaccination. Studies were excluded if they reported disease changes in only vaccinated populations or if they reported either pre-PCV or post-PCV data only.

The prespecified review outcomes were the change in incidence rates, and case counts or proportions of invasive pneumococcal disease for overall, vaccine-type grouped serotypes (seven serotypes in PCV7, ten serotypes in PCV10, six serotypes in PCV13 not in PCV7 [addPCV13], 13 serotypes in PCV13, 11 serotypes in PPV23 but not in PCV13 [addPPV23], and 23 serotypes contained in PPV23) or individual serotypes.

Two independent reviewers screened the titles and abstracts of all identified publications, of which potentially eligible publications were further reviewed at the full text screening stage. The same two reviewers independently extracted the following information from included publications into a spreadsheet: study details (author[s], publication year, country, setting, and population),

non-targeted group characteristics (eg, age, demographics, and comorbidities), vaccine programme characteristics (vaccine type, schedule, coverage, presence of a catch-up campaign, and years pre-vaccination and post-vaccination), and outcome measures (incidence, counts, or proportions of invasive pneumococcal disease). Any disagreements between the two reviewers at both screening and data extraction stages were discussed and resolved by consensus.

In the absence of a standard methodological quality assessment tool for the types of study included in this review, we used an assessment tool for before–after studies with no control group, which graded the quality of studies as good, fair, or poor.[28] The tool was tailored to our analysis by selecting seven relevant questions (appendix). For each question, a score of 1 was given if the individual study satisfied the criterion and a score of 0 otherwise. For grading each study, a total score of 0–2 was regarded as poor, 3–5 as fair, and more than 6 as good.

Data analysis

For each study and age category, we compared the invasive pneumococcal disease outcomes for the post-vaccine and pre-vaccine introduction periods. Specifically, we used the risk ratio (RR) per year post introduction as the measure of effect, calculated as invasive pneumococcal disease outcome in any epidemiological year after the introduction of the vaccine divided by invasive pneumococcal disease outcome in any epidemiological year before the introduction of the vaccine. For studies that reported disease outcomes for a number of years before and after the introduction of the vaccine, we compared every post-vaccine year invasive pneumococcal disease outcome with every pre-vaccine year. The difference between the date when post-PCV invasive pneumococcal disease was measured and the date of PCV introduction in the national programme gave the time since vaccination. In studies in which incidence was averaged for a number of years, we subtracted the year of vaccine introduction from the middle year for the period across which disease was measured to calculate the time since PCV introduction. Similarly, as in the review by Davies and colleagues,[27] to ensure comparability of invasive pneumoccal disease outcomes, for studies that reported the proportion of invasive pneumococcal disease due to grouped serotypes or individual serotypes (both vaccine type [VT] and non-vaccine type [NVT]), we used the following formula:

$$[\%VTpost \times \%NVTpre] / [\%VTpre \times \%NVTpost]$$

to approximate RR. For studies that recorded zero isolates or cases of disease after the introduction of the vaccine, we added 1 to both the numerator and the denominator to avoid a zero estimate of RR.

To model disease changes over time, we used a random-effects model that accounted for possible heterogeneity between studies and clustering within studies (appendix). We then predicted the amount of time it takes to reduce disease through herd effects by 50% and to near invasive pneumococcal disease elimination (which we defined as the time it takes to reduce disease by 90%) by using the estimated model parameters. We conducted model simulations to predict disease changes within a period of 30 years.

We also explored the effect of PCV programme characteristics such as vaccine coverage, vaccine schedule (with booster or no booster), and the presence of a catch-up campaign,[27,29,30] country-specific HIV prevalence,[31] and income (defined as low-income, middle-income, or high-income) on indirect effects. These covariates were included in a Bayesian mixed-effects model. We conducted additional continental or regional and country-specific analyses to explore the effect of any underlying source of heterogeneity on the effect of childhood PCVs on herd protection. We also did a sensitivity analysis to eliminate studies with a fair or poor quality grade, because these studies were considered to be at increased risk of bias. Additionally, we used funnel plots to detect risk of publication bias.[32]

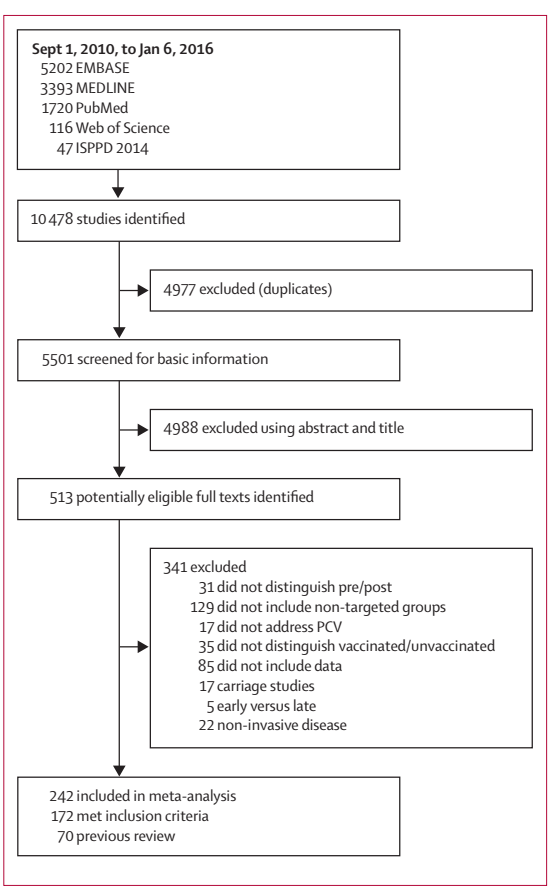

***Figure 1*: Study selection**
ISPPD 2014=International Symposium on Pneumococci and Pneumococcal Diseases 2014 conference abstracts. PCV=pneumococcal conjugate vaccine.

	Relative risk (95% CrI)	Years to 50% reduction (95% CrI)*	Years to 90% reduction (95% CrI)*
PCV7 serotypes			
Vaccine-specific serotypes (all age groups)			
4	0·77 (0·72–0·84)	2·8 (2·0–3·8)	9·1 (7·1–12·2)
6B	0·79 (0·74–0·84)	2·7 (1·9–3·6)	9·7 (7·7–12·8)
9V	0·70 (0·66–0·77)	2·5 (2·0–3·1)	7·1 (5·9–8·8)
14	0·76 (0·69–0·85)	1·9 (0·9–3·2)	8·0 (5·9–12·6)
18C	0·79 (0·73–0·86)	4·1 (3·3–5·8)	11·1 (8·8–17·0)
19F	0·84 (0·80–0·90)	5·1 (4·1–7·0)	14·7 (11·8–22·2)
23F	0·73 (0·68–0·79)	2·7 (2·1–3·4)	8·0 (6·6–10·0)
Cross-reactive serotypes (all age groups)			
6A	0·84 (0·78–0·89)	6·4 (5·0–9·3)	15·4 (11·8–23·1)
9N	1·03 (0·95–1·13)	..	..
19A	0·97 (0·84–1·15)	..	..
Age groups (all PCV7 serotypes)			
All groups	0·79 (0·75–0·81)	2·3 (1·9–2·7)	8·9 (7·8–10·3)
<5 years	0·62 (0·55–0·70)	1·2 (0·8–1·7)	4·6 (3·9–6·0)
5–18 years	0·81 (0·72–0·91)	3·1 (1·9–4·9)	10·8 (7·5–21·1)
19–49 years	0·85 (0·76–0·96)	1·9 (0·0–3·8)	11·9 (8·0–30·0)
50–64 years	0·78 (0·73–0·85)	2·7 (2·0–3·4)	9·1 (7·5–12·2)
≥65 years	0·77 (0·75–0·80)	2·6 (2·3–3·0)	8·9 (7·9–10·3)
AddPCV13 serotypes			
Vaccine-specific serotypes (all age groups)			
6A	0·87 (0·68–1·12)	0·4 (0·0–30·0)	11·9 (4·8–30·0)
1	0·76 (0·57–1·04)	2·2 (0·6–30·0)	7·8 (4·2–30·0)
3	1·03 (0·88–1·22)	30·0 (6·8–30·0)	30·0 (20·9–30·0)
5	0·59 (0·04–3·06)	0·1 (0·0–30·0)	5·7 (0·0–30·0)
7F	0·83 (0·67–1·01)	5·4 (2·9–30·0)	14·1 (7·1–30·0)
19A	0·74 (0·54–0·92)	2·9 (2·0–10·5)	7·6 (4·7–28·4)
Age groups (all addPCV13 serotypes)			
All groups	0·75 (0·64–0·87)	3·6 (2·5–6·1)	9·5 (6·1–16·6)
<5 years	0·93 (0·30–2·64)	0·0 (0·0–30·0)	13·8 (0·0–30·0)
5–18 years	0·78 (0·55–1·08)	3·0 (0·0–30·0)	9·5 (4·7–30·0)
19–49 years	0·74 (0·56–0·99)	3·1 (1·5–30·0)	8·5 (4·6–30·0)
50–64 years	0·77 (0·59–0·99)	4·3 (2·4–30·0)	10·4 (5·6–30·0)
≥65 years	0·77 (0·66–0·90)	4·1 (2·6–7·4)	10·3 (6·4–20·7)
IPD			
Age groups (all IPD)			
All groups	0·99 (0·96–0·99)	..	..
<5 years	0·97 (0·91–1·01)	..	..
5–18 years	0·97 (0·92–1·01)	..	..
19–49 years	0·95 (0·91–0·99)	..	..
50–64 years	0·96 (0·93–0·99)	..	..
≥65 years	0·97 (0·95–0·99)	..	..

CrI=credible interval. PCV=pneumococcal conjugate vaccines. PCV7=seven-valent PCV. AddPCV13=six serotypes in PCV13 not in PCV7. IPD=invasive pneumococcal disease. ..=not estimated. *Estimated from the full model including the intercept terms. The upper limits of 30 years are an artefact of following up disease changes for 30 years, suggesting that reduction will never reach 50% and 90% after this time period.

***Table 1*: Model estimates and predictions of changes in invasive pneumococcal disease among unvaccinated age groups after introduction of childhood PCV vaccination**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In our search, we identified 172 studies from 34 countries (27 high-income and seven middle-income) reporting changes in invasive pneumococcal disease (figure 1, appendix). Of these, 16 (9%) reported changes in invasive pneumococcal disease due to vaccine serotypes only (ie, either grouped PCV7, addPCV13, or PCV13 serotypes); 90 (52%) reported changes in invasive pneumococcal disease due to grouped and individual vaccine serotypes and overall disease; 60 (35%) reported changes in overall invasive pneumococcal disease only; and six (3%) focused on invasive pneumococcal disease changes due to specific individual serotypes only. 57 (33%) studies reported serotype-specific invasive pneumococcal disease changes.

In the previous systematic search by Davies and colleagues,[27] 70 studies from 11 countries reported invasive pneumococcal disease changes after the introduction of PCV7 or PCV10 into childhood immunisation programmes. 28 (40%) studies reported changes in invasive pneumococcal disease due to grouped PCV7 serotypes only; 30 (43%) reported changes in overall invasive pneumococcal disease only; 12 (17%) reported changes in disease due to both PCV7 serotypes and overall invasive pneumococcal disease; and eight (11%) studies reported serotype-specific invasive pneumococcal disease changes.

101 (42%) of the 242 included studies were done in the USA (83) and Canada (18), 91 (38%) in Europe, and only nine (4%) in low-income or middle-income countries (appendix). 17 countries implemented a 2+1 schedule (two doses plus a booster), 13 implemented a 3+1 schedule, two implemented a 3+0 schedule, and two countries had unknown schedules. 242 studies were included in the analysis of changes in overall, grouped vaccine-serotype and individual serotype-specific invasive pneumococcal disease (appendix).

Invasive pneumococcal disease due to serotypes included in PCV7 in all unvaccinated age groups significantly reduced, with little variation by individual serotype (table 1, figure 2, appendix). The overall RR of change per year in invasive pneumococcal disease caused by PCV7 serotypes was 0·79 (95% credible interval [CrI] 0·75–0·81) in all age groups combined, translating to mean periods of 2·3 years (95% CrI 1·9–2·7) to attain 50% reduction in invasive pneumococcal disease caused by PCV7 serotypes in all unvaccinated age groups and 8·9 years (7·8–10·3) to attain a 90% reduction. A similar change was observed in adults 65 years or older when the analysis was stratified by age group (RR 0·77, 95% CrI 0·75–0·80). When we assessed

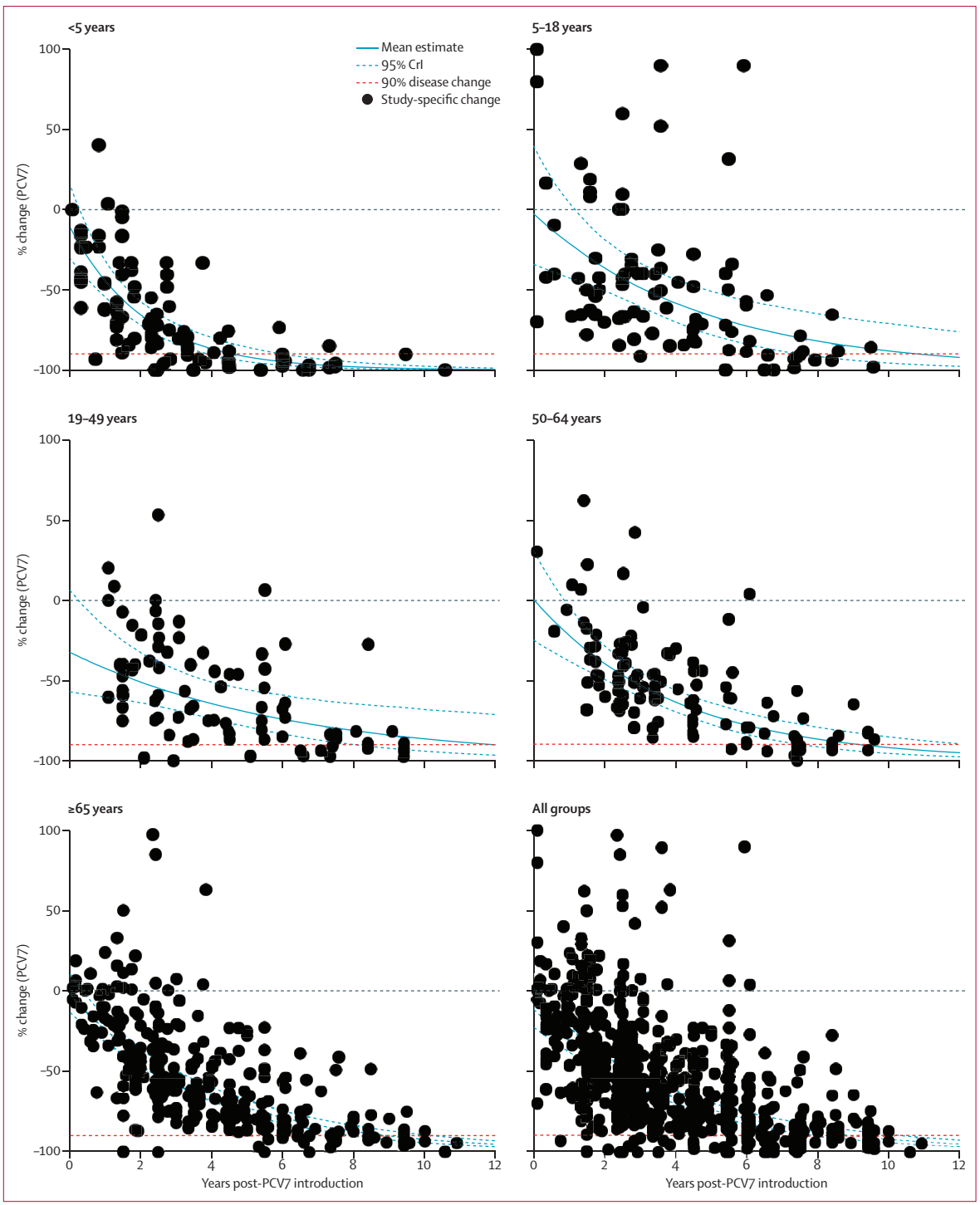

***Figure 2*: Changes in invasive pneumococcal disease due to grouped PCV7 serotypes since introduction of PCV7 into national immunisation programmes**
PCV7=seven-valent pneumococcal conjugate vaccine. CrI=credible interval.

disease changes due to additional serotypes included in the PCV13 vaccine but not in the PCV7 vaccine from the time when PCV13 replaced PCV7, the RR of disease change was 0·75 (0·64–0·87), predicting mean times to 50% disease reduction of 3·6 years (95% CrI 2·5–6·1) and 90% disease reduction of 9·5 years (6·1–16·6). We observed the same trend when grouped additional PCV13 serotypes were analysed by age category, but there were no significant changes in children 18 years or younger (table 1, figure 3, appendix). Overall invasive pneumococcal disease

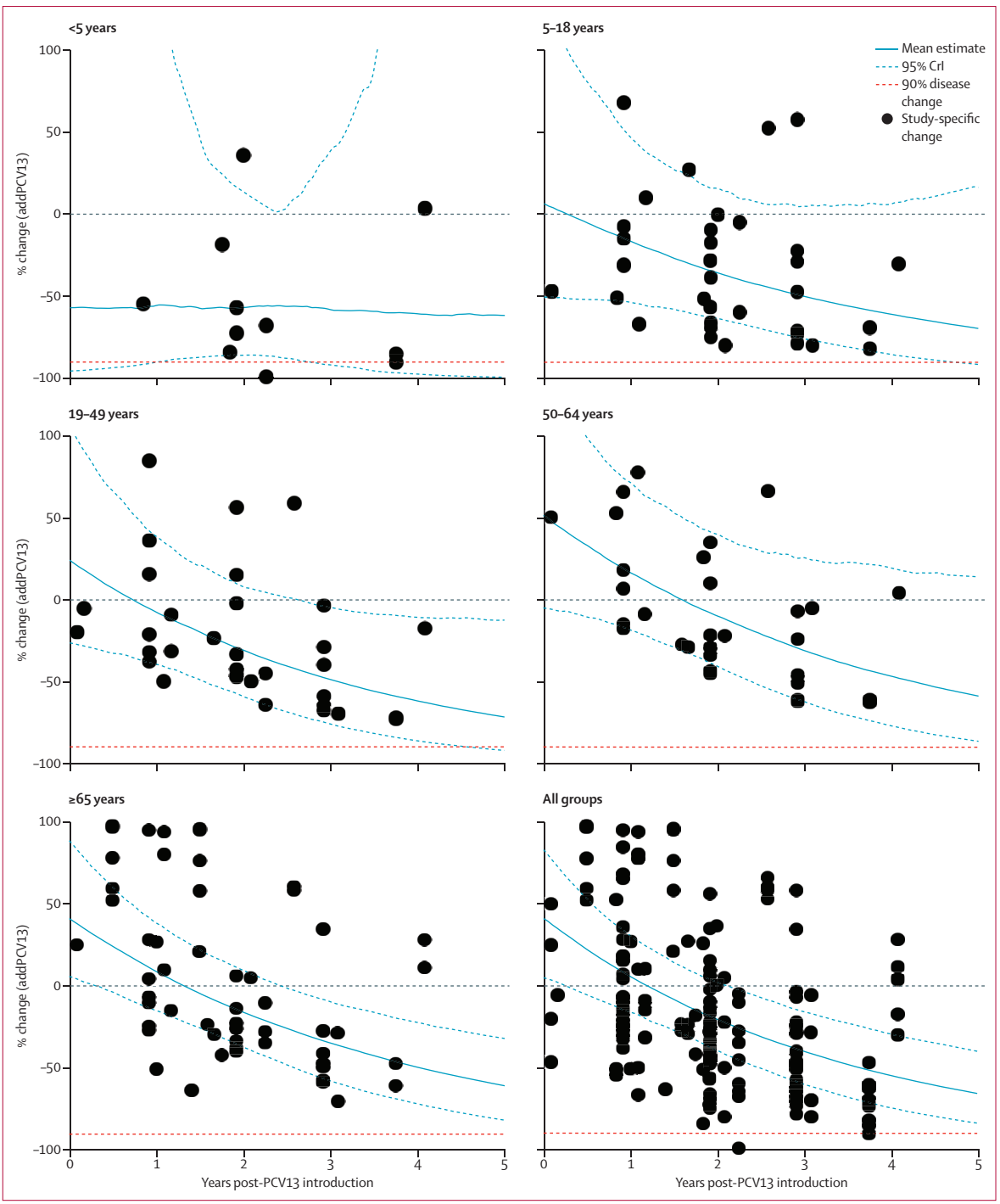

***Figure 3*: Changes in invasive pneumococcal disease due to grouped additional PCV13 serotypes after PCV13 replaced PCV7**
PCV7=seven-valent pneumococcal conjugate vaccine. PCV13=13-valent pneumococcal conjugate vaccine. addPCV13= six serotypes in PCV13 not in PCV7. CrI=credible interval.

was modestly but significantly reduced in adults older than 18 years of age, but not in those younger than 18 years (table 1, appendix).

The rate of decline of invasive pneumococcal disease due to grouped PPV23 serotypes since PCV7 introduction was similar among adults aged 19–64 years and 65 years or older (table 2). These changes were mainly driven by reductions in vaccine serotypes, presumably through indirect protection. Comparison of the changes in invasive pneumococcal disease due to grouped serotypes

	Relative risk (95% CrI), 19–64 years	Relative risk (95% CrI), ≥65 years
PCV7 serotypes		
4	0·81 (0·63–1·04)	0·76 (0·68–0·83)
6B	0·75 (0·59–0·75)	0·80 (0·75–0·86)
9V	0·78 (0·70–1·02)	0·68 (0·63–0·73)
14	0·66 (0·44–0·90)	0·75 (0·68–0·84)
18C	0·75 (0·51–1·11)	0·78 (0·71–0·86)
19F	0·87 (0·68–1·13)	0·84 (0·79–0·90)
23F	0·72 (0·55–0·91)	0·73 (0·67–0·78)
All PCV7 serotypes	0·76 (0·67–0·86)	0·79 (0·76–0·84)
Cross-reactive serotypes		
6A	0·92 (0·73–1·13)	0·83 (0·77–0·89)
9N	1·06 (0·76–1·52)	0·99 (0·93–1·11)
19A	0·87 (0·36–2·39)	0·93 (0·76–1·20)
AddPCV13 serotypes		
6A	0·68 (0·39–1·15)	0·90 (0·66–1·19)
1	0·65 (0·41–1·04)	0·81 (0·55–0·78)
3	1·11 (0·76–1·84)	1·01 (0·87–1·19)
5	0·86 (0·21–2·94)	0·24 (0·00–53·0)
7F	0·79 (0·49–1·15)	0·81 (0·63–1·08)
19A	0·76 (0·55–1·30)	0·79 (0·55–0·70)
All addPCV13 serotypes	0·75 (0·62–0·90)	0·78 (0·66–0·90)
All PCV13 serotypes	0·81 (0·71–0·90)	0·84 (0·81–0·88)
AddPPV23 serotypes		
2	No data	No data
8	1·04 (0·82–1·32)	1·04 (0·96–1·13)
9N	1·06 (0·76–1·52)	1·01 (0·93–1·11)
10A	0·85 (0·16–1·67)	1·00 (0·88–1·14)
11A	1·01 (0·74–1·39)	1·02 (0·94–1·11)
12F	0·89 (0·21–5·0)	1·07 (0·90–1·28)
15B	1·36 (0·01–424·1)	1·13 (0·90–1·38)
17F	0·94 (0·08–12·6)	1·15 (0·91–1·43)
20	1·02 (0·49–2·20)	1·01 (0·84–1·26)
22F	No data	No data
33F	1·03 (0·56–1·82)	0·95 (0·70–1·15)
All addPPV23 serotypes	1·05 (0·91–1·20)	1·02 (0·98–1·06)
All PPV23 serotypes since PCV7 introduction	0·85 (0·75–0·95)	0·87 (0·84–0·90)
Non (PPV23 + 6A)*	1·18 (0·96–1·41)	1·18 (1·12–1·25)

*All serotypes that are not covered by PPV23 and PCV13. CrI=credible interval. PCV=pneumococcal conjugate vaccines. PCV7=seven-valent PCV. PCV13=13-valent PCV. AddPCV13=six serotypes in PCV13 not in PCV7. PPV23=23-valent pneumococcal polysaccharide vaccine. addPPV23=11 serotypes in PPV23 but not in PCV13.

***Table 2*: Model estimates comparing disease changes in adults 19 years or older**

included in PCV7 and PCV13 vaccines in adults aged 19–64 years and 65 years or older, yielded similar changes in disease in the two groups (table 2). The RR of changes in invasive pneumococcal disease due to the additional six serotypes contained in PCV13, but not in PCV7 were similar between age groups (table 2). The 11 serotypes contained in PPV23 but not in PCV13 did not change invasive pneumococcal disease at any age (table 2). Disease due to serotypes not covered by existing vaccines (ie, serotypes not contained in PPV23 and PCV13), increased in adults 65 years or older (RR 1·18, 95% CrI 1·12–1·25) but not in adults aged 19–64 years (1·18, 0·96–1·41).

Model estimates did not significantly differ when studies were analysed by country (appendix). North American and European countries experienced similar changes for both invasive pneumococcal disease caused by PCV7 serotypes (RR 0·77, 95% CrI 0·73–0·81 for USA and Canada *vs* 0·77, 0·73–0·82 for Europe) and invasive pneumococcal disease due to the additional six PCV13 serotypes (0·69, 0·51–0·90 *vs* 0·77, 0·66–0·90). Model estimates did not differ when the analysis was conducted only for those studies that were graded as good (appendix). Rate of reduction in disease due to PCV7 serotypes was increased due to an increase in coverage (per percentage; RR 0·995, 95% CrI 0·989–0·998; appendix). We found no evidence of publication bias (appendix).

Discussion

In this systematic review and meta-analysis, we showed that childhood PCV immunisation confers significant indirect protection against invasive pneumococcal disease in unvaccinated population age groups due to vaccine serotypes. Herd immunity effects continued to accumulate over time and reduced disease due to PCV7 serotypes, for which follow-up data have generally been available for the longest period, with a 90% average reduction after about 9 years. The evidence from our synthesis of multicountry surveillance data shows that indirect protection against the additional six serotypes contained in PCV13 but not in PCV7 follows a similar pattern, which by extrapolation suggests that it will take a similar amount of time to achieve 90% reduction (near elimination). Overall invasive pneumococcal disease has decreased since the introduction of childhood immunisation programmes (appendix).

Our results show that the disease burden against which the PPV23 vaccine in adults is targeted might be substantially controlled by an effective mature PCV programme in children. The results show substantial and similar decreases in invasive pneumococcal disease due to PCV vaccine serotypes in adults aged 19–64 years and adults aged 65 years and older. Moreover, although disease was replaced by serotypes not covered by both PPV23 and PCV13 (corroborating previous reports[17–21]), our results did not show changes in disease due to the additional 11 serotypes contained in PPV23 but not in PCV13 in either age group, providing no evidence for serotype replacement by any of the other PPV23 strains. The lack of evidence for an increase in the 11 PPV23 types not covered in PCV13 might reflect a real biological phenomenon that removing the PCV13 strains does not advantage these serotypes. Alternatively, changes in PPV23 vaccination, such as an increase in PPV23 vaccination in those most at risk populations, might have

offered some increased protection. We had no data to identify whether such an increase might have occurred. Although PPV23 could offer some protection among older adults in whom this vaccine has been mostly used, the amount of disease directly prevented by PPV23 is probably very small.

In countries with mature paediatric PCV programmes such as Canada, Germany, the Netherlands, the UK, and the USA, invasive pneumococcal disease due to PCV7 serotypes has been nearly eliminated through indirect protection—ie, the average incidence of PCV7-invasive pneumococcal disease after nearly a decade of PCV7 use is less than 10 per 100 000 people.[9,33–37] In these countries, consistent decreases in vaccine-type adult community-acquired pneumonia (CAP) or meningitis, and non-bacteraemic CAP,[38–42] have been observed, indicating substantial indirect protection effects against non-invasive disease from childhood vaccination. Our synthesis and analysis of published data confirms the near-elimination of PCV7-invasive pneumococcal disease due to a mature childhood PCV7 programme and predicts that the residual invasive pneumococcal disease due to the additional six serotypes contained in PCV13 will be halved after a mean period of about 3 years and nearly eradicated (90% reduction) after about 9 years after the introduction of PCV13. Reduction is more rapid with higher coverage, with an estimated RR of 0·95 (95% CrI 0·89–0·98) per 10% increase in coverage. Given that countries with mature paediatric PCV programmes replaced PCV7 with PCV13 or PCV10 in 2010 or 2011, our results suggest that significant disease reduction (due to the additional six serotypes in PCV13) through indirect protection will be observed as the programme matures—ie, from the year 2017 onwards.

Decision making on large-scale PCV13 use among older adults in the presence of a mature or maturing childhood programme should consider the evidence that the vaccines are effective in adults on the one hand and that the problem against which they are targeted is disappearing due to herd immunity effects on the other. In view of the very large numbers of people aged 65 years or older, any decision to introduce PCV13 has substantial resource requirements. The evidence that vaccinating ten birth cohorts provides 90% protection to those aged 65 years or older emphasises the importance of prioritising this activity from a public health perspective. Whether an argument remains for introducing adult PCV in view of the expected near elimination of preventable disease from indirect protection should involve clinical decision making informed by cost-effectiveness assessments that might vary between countries and health-care systems.

A number of limitations to our study should be taken into account. First, we combined studies from different geographical regions that might differ in disease diagnostic methods and surveillance practices. This heterogeneity might have confounded our results. However, most studies (96%) emanated from highly industrialised nations with good surveillance programmes and broadly similar sociodemographic and socioeconomic make-up such that the epidemiology of pneumococcus is comparable among these countries. Additionally, our sensitivity analysis for individual countries and continents and our sensitivity analysis that excluded downgraded studies on the basis of their quality showed similar results to the overall estimates. Second, different studies recorded different outcome measures. Some studies measured disease incidences or cases and some studies measured the proportion of the population with the disease. Therefore, the use of an approximation formula to calculate RRs when proportions are given might underestimate the RR if the proportion of the population with non-vaccine serotype disease increased significantly, by more than 100% for example, after vaccine introduction. Some of the studies reported a single timepoint measure of disease (or an average), which does not capture secular trends. Finally, we did not have access to primary data, so we did not explicitly use the original form of data such as population sizes for use in binomial models for observed incidences. However, Thomson and Sharp[43] showed that the use of a binomial model or assuming normality of the log odds or RRs, as we did in this analysis, predominantly yields similar results.

Despite these limitations, our systematic review of 242 publications shows a largely consistent pattern across PCV serotypes that would question the merit of offering PCV13 in older age groups in the presence of established paediatric programmes, and provides quantitative estimates of the expected rate of development of herd immunity to support policy makers. An important remaining question is whether the findings are relevant to low-income countries that experience the highest levels of invasive pneumococcal disease incidence, and bear a disproportionate burden of pneumococcal disease mortality and morbidity, and where the ecology of pneumococcal transmission might be very different. Because these countries are increasingly undertaking childhood vaccination programmes, research to assess the indirect effects in these settings is particularly relevant.

Contributors

TS, NM, and SP conceptualised the project. All authors developed the search strategy for this systematic review. TS processed and analysed the data, and drafted the manuscript. All authors interpreted the results, critically reviewed the manuscript, and approved the final version of the manuscript for submission.

Declaration of interests

We declare no competing interests.

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